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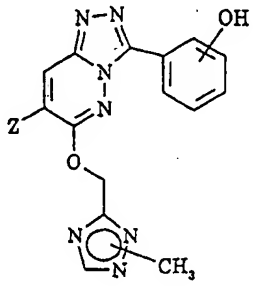

(I)

(57) Abstract

A class of substituted 1,2,4–triazolo[4,3–*b*]pyridazine derivatives of formula (I), wherein Z represents cyclobutyl or pyrrolidin–1–yl, are selective ligands for $GABA_A$ receptors, in particular having high affinity for the $\alpha 2$ and/or $\alpha 3$ subunit thereof, and are accordingly of benefit in the treatment and/or prevention of disorders of the central nervous system, including anxiety and convulsions.

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TRIAZOLO-PYRIDAZINE DERIVATIVES AS LIGANDS FOR GABA RECEPTORS

The present invention relates to a class of substituted triazolo-pyridazine derivatives and to their use in therapy. More particularly, this invention is concerned with substituted 1,2,4-triazolo[4,3-*b*]pyridazine derivatives which are ligands for $GABA_A$ receptors and are therefore useful in the therapy of deleterious mental states.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) $GABA_A$ receptors, which are members of the ligand-gated ion channel superfamily; and (2) $GABA_B$ receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual $GABA_A$ receptor subunits were cloned the number of known members of the mammalian family has grown to include at least six α subunits, four β subunits, three γ subunits, one δ subunit, one ε subunit and two ρ subunits.

Although knowledge of the diversity of the $GABA_A$ receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, a β subunit and a γ subunit constitute the minimum requirement for forming a fully functional $GABA_A$ receptor expressed by transiently transfecting cDNAs into cells. As indicated above, δ, ε and ρ subunits also exist, but are present only to a minor extent in $GABA_A$ receptor populations.

Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native $GABA_A$ receptor exists in pentameric form. The selection of at least one α, one β and one γ subunit from a repertoire of seventeen allows for the possible existence of more than 10,000 pentameric subunit combinations. Moreover, this calculation overlooks the additional

permutations that would be possible if the arrangement of subunits around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include, amongst many others, $\alpha1\beta2\gamma2$, $\alpha2\beta2/3\gamma2$, $\alpha3\beta\gamma2/3$, $\alpha2\beta\gamma1$, $\alpha5\beta3\gamma2/3$, $\alpha6\beta\gamma2$, $\alpha6\beta\delta$ and $\alpha4\beta\delta$. Subtype assemblies containing an $\alpha1$ subunit are present in most areas of the brain and are thought to account for over 40% of $GABA_A$ receptors in the rat. Subtype assemblies containing $\alpha2$ and $\alpha3$ subunits respectively are thought to account for about 25% and 17% of $GABA_A$ receptors in the rat. Subtype assemblies containing an $\alpha5$ subunit are expressed predominantly in the hippocampus and cortex and are thought to represent about 4% of $GABA_A$ receptors in the rat.

A characteristic property of all known $GABA_A$ receptors is the presence of a number of modulatory sites, one of which is the benzodiazepine (BZ) binding site. The BZ binding site is the most explored of the $GABA_A$ receptor modulatory sites, and is the site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the $GABA_A$ receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a $GABA_A$ receptor comprising the $\alpha1$ subunit in combination with a β subunit and $\gamma2$. This is the most abundant $GABA_A$ receptor subtype, and is believed to represent almost half of all $GABA_A$ receptors in the brain.

Two other major populations are the $\alpha2\beta\gamma2$ and $\alpha3\beta\gamma2/3$ subtypes. Together these constitute approximately a further 35% of the total $GABA_A$ receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha5$-containing subtype assemblies. The physiological role of these subtypes has hitherto

been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at $\alpha 1\beta\gamma 2$, $\alpha 2\beta\gamma 2$ or $\alpha 3\beta\gamma 2$ subunits will possess desirable anxiolytic properties. Compounds which are modulators of the benzodiazepine binding site of the $GABA_A$ receptor by acting as BZ agonists are referred to hereinafter as "$GABA_A$ receptor agonists". The $\alpha 1$-selective $GABA_A$ receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through $GABA_A$ receptors containing the $\alpha 1$ subunit. Accordingly, it is considered that $GABA_A$ receptor agonists which interact more favourably with the $\alpha 2$ and/or $\alpha 3$ subunit than with $\alpha 1$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Also, agents which are antagonists or inverse agonists at $\alpha 1$ might be employed to reverse sedation or hypnosis caused by $\alpha 1$ agonists.

The compounds of the present invention, being selective ligands for $GABA_A$ receptors, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; attention deficit hyperactivity disorder; and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work.

Further disorders for which selective ligands for $GABA_A$ receptors may be of benefit include pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as post-operative nausea and vomiting; eating disorders including anorexia nervosa and bulimia nervosa; premenstrual syndrome; muscle spasm or spasticity, e.g. in paraplegic patients; and hearing loss. Selective ligands for $GABA_A$ receptors may also be effective as pre-medication prior to anaesthesia or minor procedures such as endoscopy, including gastric endoscopy.

In DE-A-2741763, and in US Patents 4,260,755, 4,260,756 and 4,654,343, are described various classes of 1,2,4-triazolo[4,3-*b*]pyridazine derivatives which are alleged to be useful as anxiolytic agents. The compounds described in DE-A-2741763 and in US Patents 4,260,755 and 4,654,343 possess a phenyl substituent at the 6-position of the triazolo-pyridazine ring system. The compounds described in US Patent 4,260,756, meanwhile, possess a heteroaryl moiety at the 6- or 8-position. In none of these publications, however, is there any disclosure or suggestion of 1,2,4-triazolo[4,3-*b*]pyridazine derivatives wherein the substituent at the 6-position is attached through a directly linked oxygen atom.

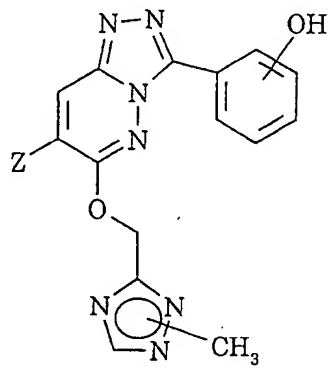
EP-A-0085840 and EP-A-0134946 describe related series of 1,2,4-triazolo[3,4-*a*]phthalazine derivatives which are stated to possess antianxiety activity. However, there is no disclosure nor any suggestion in either of these publications of replacing the benzo moiety of the triazolo-phthalazine ring system with any other functionality.

The present invention provides a class of triazolo-pyridazine derivatives which possess desirable binding properties at various $GABA_A$ receptor subtypes. The compounds in accordance with the present invention have good affinity as ligands for the $\alpha 2$ and/or $\alpha 3$ subunit of the human $GABA_A$ receptor. The compounds of this invention may interact more favourably with the $\alpha 2$ and/or $\alpha 3$ subunit than with the $\alpha 1$ subunit. Desirably, the compounds of the invention will exhibit functional

selectivity in terms of a selective efficacy for the α2 and/or α3 subunit relative to the α1 subunit.

The compounds of the present invention are $GABA_A$ receptor subtype ligands having a binding affinity (K_i) for the α2 and/or α3 subunit, as measured in the assay described hereinbelow, of 100 nM or less, typically of 50 nM or less, and ideally of 10 nM or less. The compounds in accordance with this invention may possess at least a 2-fold, suitably at least a 5-fold, and advantageously at least a 10-fold, selective affinity for the α2 and/or α3 subunit relative to the α1 subunit. However, compounds which are not selective in terms of their binding affinity for the α2 and/or α3 subunit relative to the α1 subunit are also encompassed within the scope of the present invention; such compounds will desirably exhibit functional selectivity in terms of a selective efficacy for the α2 and/or α3 subunit relative to the α1 subunit.

The present invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof:



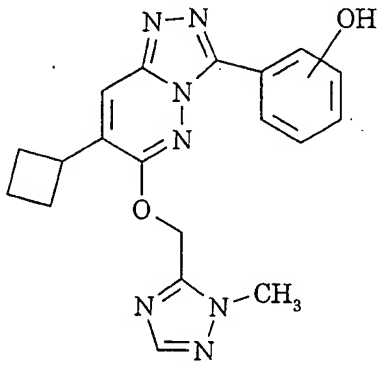
(I)

wherein Z represents cyclobutyl or pyrrolidin-1-yl.

The compounds in accordance with the present invention are encompassed within the generic scope of co-pending International Patent Application No. PCT/GB97/01946. There is, however, no specific disclosure therein of compounds corresponding to those of formula I as defined above.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

A particular sub-class of compounds according to the invention is represented by the compounds of formula II:



(II)

and pharmaceutically acceptable salts thereof.

Specific compounds within the scope of the present invention include:

4-[7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol;

3-[7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol;

2-[7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol;

4-[6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol;

and pharmaceutically acceptable salts thereof.

Also provided by the present invention is a method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

Further provided by the present invention is a method for the treatment and/or prevention of convulsions (e.g. in a patient suffering from epilepsy or a related disorder) which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

The binding affinity (K_i) of the compounds according to the present invention for the α3 subunit of the human $GABA_A$ receptor is conveniently as measured in the assay described hereinbelow. The α3 subunit binding affinity (K_i) of the compounds of the invention is ideally 10 nM or less, preferably 2 nM or less, and more preferably 1 nM or less.

The compounds according to the present invention will ideally elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor. Moreover, the compounds of the invention will ideally elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α1 subunit of the human $GABA_A$ receptor.

The potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α3 and α1 subunits of the human $GABA_A$ receptor can conveniently be measured by procedures analogous to the protocol described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, **50**, 670-678. The procedure will suitably be carried out utilising cultures of stably

transfected eukaryotic cells, typically of stably transfected mouse Ltk- fibroblast cells.

The compounds according to the present invention exhibit anxiolytic activity, as may be demonstrated by a positive response in the elevated plus maze and conditioned suppression of drinking tests (cf. Dawson *et al.*, *Psychopharmacology*, 1995, **121**, 109-117). Moreover, the compounds of the invention are substantially non-sedating, as may be confirmed by an appropriate result obtained from the response sensitivity (chain-pulling) test (cf. Bayley *et al.*, *J. Psychopharmacol.*, 1996, **10**, 206-213).

The compounds according to the present invention may also exhibit anticonvulsant activity. This can be demonstrated by the ability to block pentylenetetrazole-induced seizures in rats and mice, following a protocol analogous to that described by Bristow *et al.* in *J. Pharmacol. Exp. Ther.*, 1996, **279**, 492-501.

In order to elicit their behavioural effects, the compounds of the invention will ideally be brain-penetrant; in other words, these compounds will be capable of crossing the so-called "blood-brain barrier". Preferably, the compounds of the invention will be capable of exerting their beneficial therapeutic action following administration by the oral route.

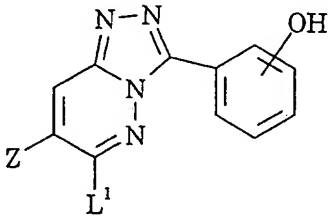
The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical

diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of anxiety, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:



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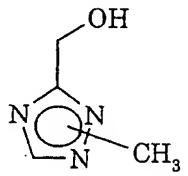


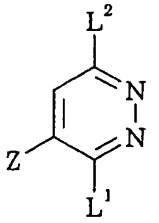
(IV)

wherein Z is as defined above, and L^1 represents a suitable leaving group.

The leaving group L^1 is typically a halogen atom, especially chloro.

The reaction between compounds III and IV is conveniently effected by stirring the reactants in a suitable solvent, typically *N,N*-dimethylformamide, in the presence of a strong base such as sodium hydride or lithium bis(trimethylsilyl)amide.

The intermediates of formula III above may be prepared by reacting a compound of formula V with a substantially equimolar amount of a hydrazine derivative of formula VI:



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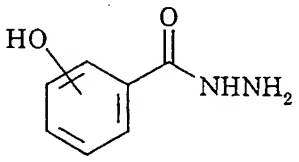


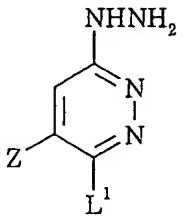
(VI)

wherein Z and L^1 are as defined above, and L^2 represents a suitable leaving group; followed, if necessary, by separation of the resulting mixture of isomers by conventional means.

The leaving group L^2 is typically a halogen atom, especially chloro. In the intermediates of formula V, the leaving groups L^1 and L^2 may be the same or different, but are suitably the same, preferably both chloro.

The reaction between compounds V and VI is conveniently effected by heating the reactants in the presence of a proton source such as triethylamine hydrochloride, typically at reflux in an inert solvent such as xylene or 1,4-dioxane.

Alternatively, the intermediates of formula III above may be prepared by reacting a hydrazine derivative of formula VII with an aldehyde derivative of formula VIII:



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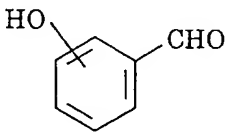


(VIII)

wherein Z and L^1 are as defined above; followed by cyclization of the intermediate Schiff's base thereby obtained.

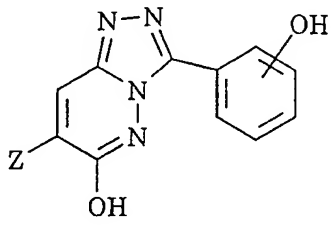
The reaction between compounds VII and VIII is conveniently effected under acidic conditions, for example in the presence of a mineral acid such as hydrochloric acid. Cyclization of the resulting Schiff's base intermediate may then conveniently be carried out by treatment with iron(III) chloride in a suitable solvent, e.g. an alcoholic solvent such as ethanol, at an elevated temperature, typically at a temperature in the region of 60°C.

The intermediates of formula VII above may be prepared by reacting the appropriate compound of formula V as defined above with

hydrazine hydrate, typically in 1,4-dioxane at the reflux temperature of the solvent; followed, if necessary, by separation of the resulting mixture of isomers by conventional means.

The reaction between compound V and hydrazine hydrate or compound VI will, as indicated above, usually give rise to a mixture of isomeric products depending upon whether the hydrazine nitrogen atom displaces the leaving group L^1 or L^2. Thus, in addition to the required product of formula III or VII, the alternative isomer will usually be obtained to some extent. For this reason it will generally be necessary to separate the resulting mixture of isomers by conventional methods such as chromatography.

In another procedure, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula IX with a compound of formula X:



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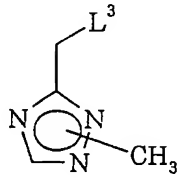


(X)

wherein Z is as defined above, and L^3 represents a suitable leaving group.

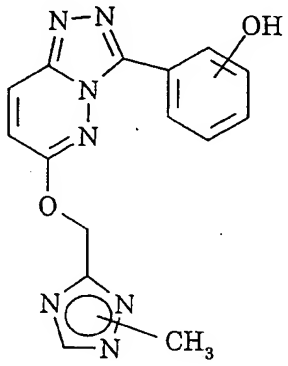
The leaving group L^3 is suitably a halogen atom, typically chloro or bromo.

The reaction between compounds IX and X is conveniently effected by stirring the reactants in a suitable solvent, typically *N,N*-dimethylformamide, in the presence of a strong base such as sodium hydride.

The intermediates of formula IX above may conveniently be prepared by reacting a compound of formula III as defined above with an

alkali metal hydroxide, e.g. sodium hydroxide. The reaction is conveniently effected in an inert solvent such as aqueous 1,4-dioxane, ideally at the reflux temperature of the solvent.

In a further procedure, the compounds of formula I wherein Z represents cyclobutyl may be prepared by a process which comprises reacting cyclobutane carboxylic acid with a compound of formula XI:



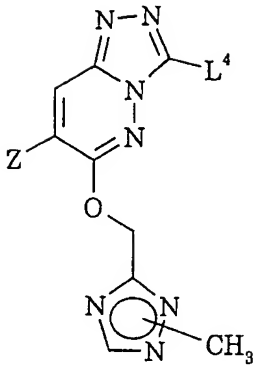
(XI)

in the presence of silver nitrate and ammonium persulphate.

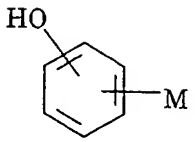
The reaction is conveniently carried out under acidic conditions in a suitable solvent, for example using sulphuric acid in water or aqueous acetonitrile, typically at an elevated temperature.

The intermediates of formula XI correspond to the compounds of formula I as defined above wherein Z is hydrogen, and they may therefore be prepared by methods analogous to those described above for preparing the corresponding compounds of formula I.

In a still further procedure, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula XII with a compound of formula XIII:



(XII)



(XIII)

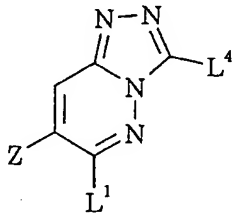
wherein Z is as defined above, M represents -$B(OH)_2$ or -$Sn(Alk)_3$ in which Alk represents a C_{1-6} alkyl group, typically *n*-butyl, and L^4 represents a suitable leaving group; in the presence of a transition metal catalyst.

The leaving group L^4 is suitably a halogen atom, e.g. bromo.

A suitable transition metal catalyst of use in the reaction between compounds XII and XIII comprises dichlorobis(triphenylphosphine)-palladium(II) or tetrakis(triphenylphosphine)palladium(0).

The reaction between compounds XII and XIII is conveniently effected in an inert solvent such as *N,N*-dimethylformamide, typically at an elevated temperature.

The intermediates of formula XII may be prepared by reacting a compound of formula IV as defined above with a compound of formula XIV:



(XIV)

wherein Z, L^1 and L^4 are as defined above; under conditions analogous to those described above for the reaction between compounds III and IV.

The intermediates of formula IV above may be prepared by the procedures described in EP-A-0421210, or by methods analogous thereto.

Where they are not commercially available, the starting materials of formula V, VI, VIII, X, XIII and XIV may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention potently inhibit the binding of [^{3}H]-flumazenil to the benzodiazepine binding site of human $GABA_A$ receptors containing the $\alpha 2$ or $\alpha 3$ subunit stably expressed in Ltk- cells.

Reagents

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH_2PO_4, 100 mM KCl, pH 7.4 at room temperature.
- [^{3}H]-Flumazenil (18 nM for $\alpha 1\beta 3\gamma 2$ cells; 18 nM for $\alpha 2\beta 3\gamma 2$ cells; 10 nM for $\alpha 3\beta 3\gamma 2$ cells) in assay buffer.
- Flunitrazepam 100 μM in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

Harvesting Cells

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 µl of assay buffer.
- 50 µl of [^{3}H]-flumazenil (final concentration for $\alpha1\beta3\gamma2$: 1.8 nM; for $\alpha2\beta3\gamma2$: 1.8 nM; for $\alpha3\beta3\gamma2$: 1.0 nM).
- 50 µl of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10 µM final concentration.
- 100 µl of cells.

Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of [^{3}H]-flumazenil from the $\alpha2$ and/or $\alpha3$ subunit of the human $GABA_A$ receptor of 100 nM or less.

EXAMPLE 1

4-[7-Cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol

a) 3,6-Dichloro-4-cyclobutylpyridazine

3,6-Dichloropyridazine (10 g) was suspended in water (200 ml), H_2SO_4 (19.7 g) and cyclobutane carboxylic acid (32.7 g) were added and the reaction degassed under N_2 at 70°C. Silver nitrate (2.28 g) was added followed by dropwise addition of ammonium persulfate (45.9 g) in water (120 ml). After an additional 1 hour heating at 70°C, the reaction was poured onto ice, basified to pH 8-9 with aqueous ammonium hydroxide and extracted into ethyl acetate (3 x 500 ml), dried ($MgSO_4$) and evaporated to dryness. Purified with hexane-ethyl acetate mixtures to obtain pure product (13.4 g). ^{1}H NMR (360MHz, $CDCl_3$) δ 1.57 (2H, m), 1.82 (4H, m), 2.20 (1H, m), 3.30 (1H, m), 7.38 (1H, s); MS (ES^+) m/e 217 $[MH]^+$.

b) 3-Chloro-4-cyclobutyl-6-hydrazinopyridazine

3,6-Dichloro-4-cyclobutylpyridazine (22.5 g, 0.11 mol) and hydrazine hydrate (34 ml, 0.66 mol) were heated at reflux in dioxan (280 ml) for 24 hours. Upon cooling the desired isomer crystallized from the reaction and was collected by filtration (13.3 g, 64%). ^{1}H NMR (250 MHz, d_6-DMSO) 1.68-1.86 (1H, m), 2.00-2.11 (3H, m), 2.29-2.38 (2H, m), 3.52-3.61 (1H, m), 4.35 (2H, br), 6.99 (1H, s), 8.06 (1H, br); MS (ES^+) m/e 198 $[MH]^+$, 200 $[MH]^+$.

c) 4-(6-Chloro-5-cyclobutylpyridazin-3-ylhydrazonomethyl)phenol

3-Chloro-4-cyclobutyl-6-hydrazinopyridazine (0.50 g, 2.5 mmol) and 4-hydroxybenzaldehyde (0.31 g, 2.5 mmol) were stirred in 0.2M hydrochloric acid (15 ml) for 2 hours. The precipitated imine was then

collected by filtration and dried to give the title compound (0.63 g, 83%). MS (ES^+) 305 $[MH]^+$, 303 $[MH]^+$.

d) 4-(6-Chloro-7-cyclobutyl-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)phenol

Ferric chloride (2.84 g, 10.5 mmol) in ethanol (50 ml) was added dropwise to a solution of the foregoing imine (1.06 g, 3.5 mmol) in ethanol (60 ml) heated at 60°C. After 6 hours the reaction mixture was partitioned between dichloromethane (250 ml) and brine (250 ml). The organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica gel, eluting with ethyl acetate-hexane mixtures to afford the title *phenol* (0.42 g, 67%). ^1H NMR (360 MHz, d_6-DMSO) 1.80-1.90 (1H, m), 1.98-2.06 (1H, m), 2.20-2.30 (2H, m), 2.34-2.42 (2H, m), 3.66-3.70 (1H, m), 6.97 (2H, d, J = 8.7 Hz), 8.14 (2H, d, J = 8.8 Hz), 8.31 (1H, d, J = 1.4 Hz), 10.1 (1H, br s). MS (ES^+) 303 $[MH]^+$, 301 $[MH]^+$.

e) 4-[7-Cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol

Sodium hydride (60% dispersion in oil, 34 mg, 0.71 mmol) was added to a solution of (2-methyl-2*H*-1,2,4-triazol-3-yl)methanol (82 mg, 0.71 mmol) (prepared as in EP-A-421210) in dry DMF (2 ml) at room temperature. After 1 h at room temperature a solution of the foregoing phenol (214 mg, 0.7 mmol) was added and the reaction stirred for 18 hours. The residue was partitioned between dichloromethane and water. The aqueous was further extracted with dichloromethane (2 x 100 ml). The combined extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica gel, eluting with 0-2% ethyl acetate-methanol to afford the title *phenol* (160 mg, 60%). ^1H NMR (360MHz, d_6-DMSO) δ 1.65-1.87 (1H, m), 1.95-2.09 (1H, m), 2.18-2.32 (4H, m), 3.53-3.63 (1H, m), 3.92 (3H, s), 5.64 (2H, s), 6.96 (2H, d, J = 8.8 Hz),

7.98 (1H, s), 8.08 (1H, s), 8.19 (2H, d, J = 8.8 Hz), 10.0 (1H, s). MS (ES^+) m/e 378 $[MH]^+$.

EXAMPLE 2

3-[7-Cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol

Prepared in an analogous procedure as outlined in Example 1 Steps c), d) and e) using 3-hydroxybenzaldehyde in Step c) to afford the title *phenol*. ^{1}NMR (360MHz, d_6-DMSO) δ 1.75-1.87 (1H, m), 1.95-2.09 (1H, m), 2.17-2.32 (4H, m), 3.54-3.65 (1H, m), 3.93 (3H, s), 5.66 (2H, s), 6.92 (1H, q, J = 7.9, 1.7 Hz), 7.38 (1H, t, J = 7.9 Hz), 7.83 (1H, d, J = 7.7 Hz), 7.87 (1H, d, J = 2.1 Hz), 7.99 (1H, s), 8.13 (1H, d, J = 1.4 Hz). MS (ES^+) m/e 378 $[MH]^+$.

EXAMPLE 3

2-[7-Cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol

Prepared in an analogous procedure as outlined in Example 1 Steps c), d) and e) using 2-*tert*-butyldimethylsilyloxybenzaldehyde (prepared as described in *J. Chem. Soc., Perkin Trans. I*, 1988, 1417-1423) in Step c) to afford the title *phenol*. ^{1}NMR (250MHz, $CDCl_3$) δ 1.87-1.97 (1H, m), 2.09-2.25 (3H, m), 2.34-2.45 (2H, m), 3.56-3.70 (1H, m), 4.04 (3H, s), 5.65 (2H, s), 6.98 (1H, dt, J = 8.0, 1.2 Hz), 7.14 (1H, dd, J = 8.2, 1.1 Hz), 7.37 (1H, dt, J = 8.5, 1.5 Hz), 7.84 (1H, d, J = 1.5 Hz), 7.96 (1H, s), 8.64 (1H, dd, J = 8.3, 1.1 Hz), 11.89 (1H, s). MS (ES^+) m/e 378 $[MH]^+$.

EXAMPLE 4

4-[6-(2-Methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol

a) 4-Bromo-1,2-dihydropyridazine-3,6-dione

Hydrazine hydrate (28 ml, 576 mmol) was added dropwise to a stirred solution of bromomaleic anhydride (100 g, 565 mmol) in THF (1 l) cooled in an ice-bath so that the internal temperature did not exceed 10°C. After complete addition of the hydrazine the mixture was refluxed for 18 h. Solvent was removed by evaporation and the residues were dried by azeotroping with toluene. The residue was triturated and washed with diethyl ether to give the title compound as an orange solid (83 g, 77%). ^{1}H NMR (250 MHz, d_6-DMSO) δ 7.68 (1H, br s). MS (ES^+) m/e 193 $[MH]^+$, 191 $[MH]^+$. This material was used without further purification.

b) 4-Bromo-3,6-dichloropyridazine

A solution of 4-bromo-1,2-dihydropyridazine-3,6-dione (10 g, 52 mmol) in phosphorus oxychloride (100 ml) was stirred and heated at 100°C under nitrogen for 16 hours. Upon cooling the excess phosphorus oxychloride was removed *in vacuo*. The residue was azeotroped with toluene (x2), then taken up in dichloromethane/water. The mixture was carefully basified with sodium hydrogen carbonate (solid). It was necessary to dilute the mixture further to get two clear layers. The two layers were separated and the aqueous was extracted with dichloromethane (x3). The combined extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica gel, eluting with dichloromethane to afford the title *pyridazine* (5.0 g, 42%) as a colourless solid. ^{1}H NMR (250 MHz, $CDCl_3$) 7.68 (br s). MS (ES^+) 230 $[MH]^+$, 228 $[MH]^+$.

c) 3,6-Dichloro-4-(pyrrolidin-1-yl)pyridazine

Pyrrolidine (3.36 ml, 40 mmol) was added to a stirred solution/suspension of 4-bromo-3,6-dichloropyridazine (8.3 g, 36 mmol) and potassium carbonate (13.8 g, 0.1 mol) in dry DMF (100 ml) at room temperature under nitrogen. The mixture was stirred at room temperature for 16 hours, then at 60°C for 3 hours. The reaction was poured into water (250 ml). The aqueous was extracted with ethyl acetate (x3). The combined extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica gel, eluting with 0.5% methanol/dichloromethane to afford the title *pyridazine* (7.2 g, 92%) as a colourless oil. ^1H NMR (250 MHz, $CDCl_3$) 2.00-2.05 (4H, m), 3.61-3.69 (4H, m), 6.46 (1H, s). MS (ES^+) 218 $[MH]^+$, 220 $[MH]^+$.

d) 3-Chloro-6-hydrazino-4-(pyrrolidin-1-yl)pyridazine

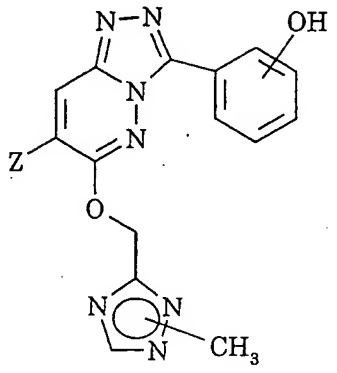
3,6-Dichloro-4-(pyrrolidin-1-yl)pyridazine (7.2 g, 33 mmol) and hydrazine hydrate (9.96 g, 0.2 mol) were heated at reflux in dioxan (130 ml) for 6 hours. Upon cooling the desired isomer crystallized from the reaction and was collected by filtration (4.1 g, 58%). ^1H NMR (250 MHz, d_6-DMSO) 1.79-1.84 (4H, m), 3.25-3.40 (4H, m), 4.12 (2H, br), 6.09 (1H, s), 7.47 (1H, s). MS (ES^+) 214 $[MH]^+$, 216 $[MH]^+$.

e) 4-[6-(2-Methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol

This compound was prepared as described in Example 1 Steps c), d) and e) except using 3-chloro-6-hydrazino-4-(pyrrolidin-1-yl)pyridazine instead of 3-chloro-4-cyclobutyl-6-hydrazinopyridazine in Step c). Data for the title compound: ^1H NMR (360 MHz, $CDCl_3$) 1.97-2.04 (4H, m), 3.50-3.56 (4H, m), 3.95 (3H, s), 5.06 (2H, s), 6.66 (1H, s), 6.95-7.03 (2H, m), 7.41 (1H, s), 7.96-8.04 (3H, m); MS (ES^+) 393 $[MH]^+$.

CLAIMS:

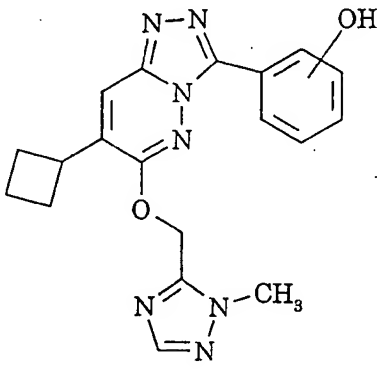
1. A compound of formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein Z represents cyclobutyl or pyrrolidin-1-yl.

2. A compound as claimed in claim 1 represented by formula II:



(II)

and pharmaceutically acceptable salts thereof.

3. A compound selected from:

4-[7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol;

3-[7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol;

2-[7-cyclobutyl-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol;

4-[6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-7-(pyrrolidin-1-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]phenol;

and pharmaceutically acceptable salts thereof.

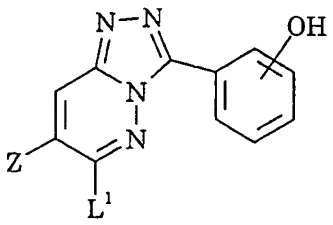
4. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.

5. The use of a compound as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment and/or prevention of anxiety.

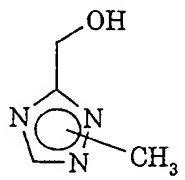
6. The use of a compound as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment and/or prevention of convulsions.

7. A process for the preparation of a compound as claimed in claim 1, which comprises:

(A) reacting a compound of formula III with a compound of formula IV:



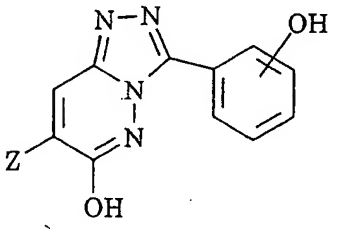
(III)



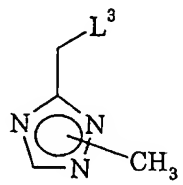
(IV)

wherein Z is as defined in claim 1, and L^1 represents a suitable leaving group; or

(B) reacting a compound of formula IX with a compound of formula X:



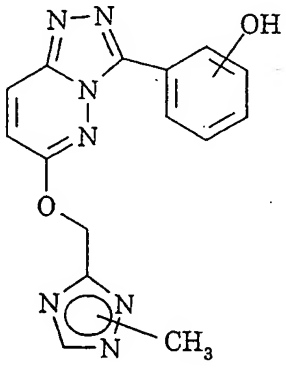
(IX)



(X)

wherein Z is as defined in claim 1, and L^3 represents a suitable leaving group; or

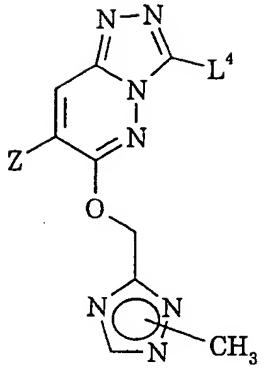
(C) reacting cyclobutane carboxylic acid with a compound of formula XI:



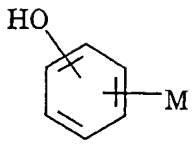
(XI)

in the presence of silver nitrate and ammonium persulphate; or

(D) reacting a compound of formula XII with a compound of formula XIII:



(XII)



(XIII)

wherein Z is as defined in claim 1, M represents $-B(OH)_2$ or $-Sn(Alk)_3$ in which Alk represents a C_{1-6} alkyl group, and L^4 represents a suitable leaving group; in the presence of a transition metal catalyst.

8. A method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof.

9. A method for the treatment and/or prevention of convulsions which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/GB 99/00108

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 A61K31/50 A61K31/41 //C07D478/04,249:00,237:00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 085 840 A (LEPETIT SPA) 17 August 1983 cited in the application see page 69 - page 71; example 1 see page 61, line 1 - page 66, line 12 ---	1-9
A	GB 1 589 237 A (AMERICAN CYANAMID CO) 7 May 1981 cited in the application see page 32 - page 33; claim 1 see page 8, line 14 - page 10, line 4 ---	1-9
P,X	WO 98 04559 A (GUIBLIN ALEXANDER RICHARD ;MERCK SHARP & DOHME (GB); MOORE KEVIN W) 5 February 1998 cited in the application see page 181 - page 201; claims -----	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 1999	07. 05. 99

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

...ternational application No.
PCT/GB 99/00108

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8 and 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONA EARCH REPORT

Information on patent family members

Inte...ational Application No
PCT/GB 99/00108

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